REMARKS

I. Claim amendments

Claims 1, 3 and 22 are amended to recite cyclic administration, *i.e.*, administration of a drug for a period of time followed by rest. This amendment is supported by the specification as originally filed, *e.g.*, page 35, line 32 and page 36, line 26. No new matter is added. After this Amendment, claims 1, 3, 5-9, 11, 15, 22, and 41-47 will be pending.

II. The instant claims are not obvious under 35 U.S.C. §103

The Office has rejected the instant claims under 35 U.S.C. §103 as follows:

- rejected claims 1, 5, 15, 22 and 41-47 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* (*Cancer Chemotherapy and Pharmacology* (2002) 50:237-242, "Tsimberidou *et al.*") in view of Man *et al.* (WO2001/34606, "Man *et al.*");
- rejected claims 6 and 11 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Canepa *et al.* (*British Journal of Haematology* (2001) 115:313-315, "Canepa *et al.*"); and
- rejected claims 3 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Alter *et al.* (*Blood* (1985) 66:373-379, "Alter *et al.*").

Applicant respectfully disagrees with each of these rejections for the following reasons and requests reconsideration.

1. Claims 1, 5, 15, 22 and 41-47 are not *pima facie* obvious

The Office Action states that Tsimberidou *et al.* teaches a method of treating agnogenic myeloid metaplasia (AMM) with Etanercept that inhibits TNF-α activity, and Man *et al.* teaches that the instant claimed compound, {2-[(1 S)-I-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide ("Compound A") is a TNF-alpha inhibitor. Office Action, pages 5-7. On this basis, the Office Action alleges that it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (Etanercept) for another (Compound A) with an expectation of

success, since the prior art establishes that both function in similar manner. See pages 7-8 of the Office Action. Applicant respectfully disagrees.

A. The Cited Art would Not have Provided any Reason to Pursue the Claimed Invention

The rejection is based the allegation that Tsimberidou *et al.* teaches a method of treating AMM with TNF-α inhibitors such as Etanercept and Man *et al.* teaches the instant compound as a TNF-α inhibitor. Pages 6-7 of the Office Action. Applicant submits an article evidencing that the Office cannot rely on TNF-α activity to support the current rejection. (*See* Ramanarayanan submitted herewith (Exhibit 1)). The authors reviewed literature of phase I and II studies involving anti-TNF-therapy, and explored the activity and tolerance of TNF-α inhibitors in various hematological malignancies including MPD. They reported that Etanercept as a single agent did not yield significant responses. The authors concluded that anti-TNF-α therapy by itself does not induce therapeutic response and that combination therapy with TNF-α inhibitors has to be evaluated to determine their role in MPD. Thus, not all TNF-α inhibitors treat MPD, and the rejection fails.

Further, Tsimberidou *et al.* teaches away from the claimed invention. Tsimberidou *et al.* reports that no responses were seen with Etanercept treatment (pages 237 and 240, second column). Tsimberidou *et al.* also states that current treatments other than: allogenic stem cell transplantation, including hydroxyurea, alpha-interferon, androgens, thalidomide, and splenectomy are ultimately ineffective in AMM patients (page 240, 1st column). The phrase "other than" means that the treatments using compounds cited after the phrase, but nothing else, are effective against AMM. Because the instant compound is not one of the cited compounds after the phrase "other than," Tsimberidou et al. teaches that the instant compound is not effective against AMM. Thus, for purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. "[A]n applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In *re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). (Emphasis added.) *See also In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (noting that a showing "that the art in any material respect taught away from the claimed invention" can rebut an obviousness allegation) (internal quotation marks omitted); see also M.P.E.P. § 2141.02(VI) ("A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.").

In addition, the amendments to the claims render the claims patentable. As amended herein, the instant claims recite, *inter alia*, a very specific method of treating specific myeloproliferative disease ("MPD," polycythemia rubra vera, primary thrombocythemia, chronic myelogenous leukemia, or agnogenic myeloid metaplasia) that comprises cyclically administering specific amounts (about 5 to 50 mg/day) of a specific compound {2-[(1 S)-I-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide ("instant compound"). In view of the instant amendments, the Office's rejections are now moot. Indeed, the limitations of the instant claims, when considered in combination, render the instant claims non-obvious over the cited art under 35 U.S.C. §103. The cited art does not provide any reason to pursue the very unique and specific MPD treatment method as claimed. The cited references are devoid of any meaningful predictive value with respect to the claimed method that requires at least: (1) using the specific amounts (5 to 50 mg/day) of the recited compound for treating specific MPD, and (2) by cyclically administering it in particular dosing regimens. These claim elements are not taught or suggested in the cited art.

Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole. That is, all the claim elements must be considered in a 103 rejection. *Abbott Laboratories v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2008). Cited art simply fails to do so. Indeed, the Office recognizes that Tsimberidou *et al.* does not teach the use of the instant compound in the recited amount for treating any MPD. Office Action, page 6.

Man does not cure this deficiency since it is silent as to the use of the recited compound in treating any MPD. The Examiner has provided no specific source of motivation to combine the teachings of the references for the particular claimed cyclic therapy. Therefore, the instant rejection amounts to the mere allegation of a motivation to combine the cited references, simply because some, but not all, of the elements of the instant claims are present individually in the references. This does not meet the legal requirement for a *prima facie* case of obviousness. *Abbott*, 544 F.3d at 1351; *see also Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). In this case, there is no motivation to combine the teachings of the cited art in the claimed method for treating specific MPD using the specific amounts (5 to 50 mg/day) of the recited compound by cyclically administering them in particular dosing regimens.

The Office Action, however, alleges that dose optimization is routine practice in the pharmaceutical art. Office Action, page 7. In this regard, it appears the Office Action takes the position that all dosage regimens are *per se* obvious. This inflexible approach to an obviousness determination was expressly prohibited in *KSR*, where the Supreme Court stated that "when a court transforms [a] general principle into a rigid rule that limits the obviousness inquiry...it errs." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). *See also* MPEP §2144.07 ("Use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. §103").

Indeed, courts have held claims reciting dosage limitations to be non-obvious when the prior art provides no basis to pursue the recited dosage. *See, e.g., In re Wiggins*, 397 F.2d 356, 360 (C.C.P.A. 1968) (reversing Board's rejection of composition claim reciting dosage limitation in part because of prior art's "failure to suggest appellant's claimed dosage amounts."); *Ex parte Boden*, 2008 WL 5376662; *Ex parte Eisenhardt*, No. 1999-1229, 2002 WL 1801461 at *4 (Bd. Pat. App. & Interf. 1999) (reversing in part examiner's obviousness rejection of composition claims because dosage limitations were not addressed); *Ex Parte Woldemussie*, No. 95-4823, 1995 WL 1696895 (Bd. Pat. App. & Interf. 1995) (unpublished decision) (reversing examiner's obviousness rejection of claims to method of administering a composition comprising specific doses, stating that "the examiner should determine whether it would have been obvious to one of ordinary skill in the art to adjust the dosage to a value within the claimed range."); *Ex Parte Pickar*, No. 2004-1478, 2004 WL 4983341 at *2 (Bd. Pat. App. & Interf. 2004) (unpublished decision) (reversing in part examiner's obviousness rejection because "the examiner has pointed to nothing in the [cited] reference that suggests the dosage range recited in [the] claim....").

To say that the development of a dosage or dosage regimen is routine is an oversimplification of drug development and belittles the significance of successfully developing a dosage or dosage regimen. The successfully development of a dosage or dosage regimen is an inventive contribution that is the product of time, effort expense, and ingenuity, which should not be glossed over as a mere "routine" act.

Even if the act of administering a particular dosage or dosage regimen is within the purview of a skilled artisan, there still needs to be reason for that skilled artisan to pursue the particular dosage or dosage regimen in the first place. Indeed, for a determination of obviousness, it is important to identify a reason that would have prompted a person of

ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *KSR*, 127 S.Ct. at 1741. In the context of the instant claims, even if a skilled artisan could routinely perform the claimed dosage regimen, that skilled artisan would not be able to predict, absent teachings to the contrary, whether any particular dosage regimen would actually be effective without the benefit of hindsight. Under *KSR*, the hallmark of a proper obviousness determination is predictability, which the cited references do not provide.

Further, Tsimberidou *et al.* discloses that Etanercept at a dosage of 25 mg *weekly* was well tolerated (page 240, 2nd column). Thus, Tsimberidou *et al.* teaches away from the claimed methods using the recited amounts (5 to 50 mg per day) of the instant compound in treating MPD.

In view of the foregoing, a *prima facie* case of obviousness has not been established and the rejection under 35 U.S.C. § 103(a) be withdrawn.

B. No Reasonable Expectation of Success exists

Further, assuming that the Patent Office is correct and the use of TNF-α inhibitor in treating MPD is suggested by the cited art, the PTO has not presented evidence to demonstrate that the prior art provides the required reasonable expectation of success. Tsimberidou *et al.* concludes that no responses were seen with Etanercept treatment (pages 237 and 240, 2nd column). More importantly, Applicant submitted a publication showing that anti-TNF-α therapy by itself including Etanercept does not induce therapeutic response in treating MPD (see Ramanarayanan submitted herewith). In view of this teaching, one of ordinary skill in the art would not expect that every compound demonstrating TNF-α inhibition would be useful in treating MPD. Without more specific guidance in the art, no reasonable expectation exists to use the specific compound of the instant methods for the treatment of MPD. *KSR*, 127 S.Ct. at 1739 and 1742 (an obviousness determination takes into account whether the combination of elements would yield "anticipated success" or "predictable results"). Further, the courts have long recognized the unpredictability of the biological properties of chemical compounds. *See, e.g., In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties..."). Thus, because the Patent Office has not presented evidence of a reasonable expectation of success, a *prima facie* case of obviousness has not been made.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 1, 5, 15, 22 and 41-47 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.*

2. The Rejection of Claim 11 Should Be Withdrawn

On page 9 of the Office Action, the PTO states that claim 11 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* as applied to claims 1, 5, 15, 22 and 41-47 above, and further in view of Canepa *et al.*, because it teaches primary or secondary MPD. Applicant respectfully disagrees.

Claim 11 depends on claim 1 or 3, and further recites "wherein the myeloproliferative disease is primary or secondary." Since claim 1 or 3 is not obvious over Tsimberidou *et al.* in view of Man *et al.* for the reasons discussed above, claim 11 is also not obvious over Tsimberidou *et al.* in view of Man *et al.*

Canepa *et al.* does not cure the defects of Tsimberidou *et al.* and Man *et al.* Canepa *et al.* merely discloses the use of thalidomide to MMM patients who were administered in 200 mg per day increased to 800 mg per day (page 314, 1st column). It describes that all secondary MMM failed to respond and the efficacy in the different phases of the disease must be further evaluated (page 313). Further, it does not teach or suggest specific methods for treating specific MPD with the recited compound, much less using about 5-50 mg of the instant compound by cyclic administration. Therefore, all elements of claim 11 are not taught or suggested by the cited art in combination. Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole. *Abbott Laboratories v. Sandoz, Inc.*, at 1351 (Fed. Cir. 2008).

In view of the foregoing, a *prima facie* case of obviousness has not been established and this rejection be withdrawn.

3. Claims 3 and 7-9 are not obvious

On page 10 of the Office Action, the Examiner maintained the rejection of claims 3 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* as applied to claims 1, 5, 15, 22 and 41-47 above, and further in view of Alter *et al.* Applicant respectfully disagrees.

Claim 3 recites all limitations of claim 1 plus the recitation of "and a therapeutically or prophylactically effective amount of at least one second active agent." Since claim 1 is not obvious over Tsimberidou *et al.* in view of Man *et al.* for the reasons discussed above, claim 3 and claims 7-9, which depend on claim 3 directly or indirectly, are also not obvious over Tsimberidou *et al.* in view of Man *et al.*

Alter *et al.* adds nothing to Tsimberidou *et al.* and Man *et al.* Alter *et al.* studied the effects of hydroxyurea on hemoglobin F in MPD patients. It does not teach or suggest the use of the combination with any particular drug in specific amounts, for the treatment of specific MPD, much less the combination therapy of using the recited compound by cyclic dosing regimen. It provides no insight as to the feasibility of combination treatment. Thus, the cited art would not have provided any basis to predict whether the combination with the instant compound could be effective for the treatment of specific MPD. The PTO has failed to establish that each of claim limitations is taught or suggested in the prior art, as required for a *prima facie* case of obviousness. *See, e.g. Abbott Laboratories v. Sandoz, Inc.*, at 1351 (Fed. Cir. 2008).

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 3 and 7-9.

4. The Rejection of Claims 6 Should Be Withdrawn

On pages 11-12 of the Office Action, the Examiner maintained the rejection of claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* as applied to claims 1, 5, 15, 22 and 41-47 above, and further in view of Canepa *et al.*. Applicant respectfully disagrees.

Claim 6 depends on claim 1 or 3, and further recites that the patient is refractory to MPD treatment using thalidomide. Since claim 1 or 3 is not obvious over Tsimberidou *et al.* in view of Man *et al.* for the reasons discussed above, claim 6 is also not obvious over Tsimberidou *et al.* in view of Man *et al.*

Canepa *et al.* adds nothing to change the errors in the rejection already pointed out. The PTO alleges that Canepa *et al.* teaches that thalidomide has been effectively used for the treatment of MPD (page 11 of the Office Action). If the PTO's allegation is true that thalidomide was effective in treating MPD, the patient would not be refractory to MPD

treatment using thalidomide. However, claim 6 recites that the patient is refractory to MPD treatment using thalidomide. Thus, Canepa *et al.* cannot render the claim obvious.

Further, Canepa *et al.* does not provide any reason to pursue the specific method using the specific amounts (5 to 50 mg/day) of the recited compound for treating specific MPD, by cyclically administering them in particular dosing regimens. Therefore, Canepa *et al.*, individually or in combination with Tsimberidou *et al.*, Man *et al.*, does not teach or suggest all recitations of claim 6. In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claim 6.

CONCLUSION

In light of the above amendments and remarks, Applicant respectfully requests that the Examiner reconsider this application with a view towards allowance. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: **April 8, 2010**

by: Yeahsil Moon Reg. No. 52,042
For: Anthony M. Insogna (Reg. No. 35,203)

Jones Day
222 East 41st Street
New York, N.Y. 10017-6702
Tel: 212-326-3778